

## **REMARKS**

Reconsideration of this application is respectfully requested.

### **I. Status of the claims**

Claims 1, 3-6, and 8-11 were pending in this application. Claims 3-6 were amended to correct for typographical errors and new claims 14 to 16 were added to further clarify the invention. Support for the amendments and new claim can be found in the application as originally filed. Support for new claim 14 can be found in page 2, lines 6-8 and page 8, lines 16-21. Support for new claim 15 can be found in claims 1 and 11. Support for claim 16 can be found, for instance, at page 10, lines 14-19. Accordingly, no new matter has been added to the application as a result of the present amendment.

### **II. Associate Power of attorney**

Applicants submit herewith an associate Power of Attorney for Emily Miao, Anita J. Terpstra, and Paul H. Berghoff of the law firm of McDonnell Boehnen Hulbert & Berghoff (Customer no. 020306) from an attorney or agent of record. Accordingly, Emily Miao is now an attorney of record via the associate Power of Attorney document.

### **III. Rejection under 35 U.S.C. § 112, first paragraph (Written Description)**

Claims 1, 3-6 and 8-10 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of written description. Specifically, the Examiner alleged that the genus of nucleic acids encoding a *Rhodospiridium* cephalosporin C esterase is represented by a genomic nucleic acid isolated from a single strain of *Rhodospiridium toruloides* (ATCC 10657) having the nucleotide sequence of SEQ ID NO:1 and corresponding cDNA having the sequence of SEQ ID NO:3. The Examiner asserts that no other nucleic acid sequences encoding a *Rhodospiridium* cephalosporin esterase is described. The Applicants respectfully traverse this rejection.

According to the revised written description guidelines, “‘The ‘essential goal’ of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed.’” Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, “Written Description” Requirement, 66 FR 1099, 1104, Jan. 5, 2001 (quoting *In re Barker*, 559 F.2d 588, 592 n.4 (CCPA 1977)). The

written description requirement is a factual issue that involves the question of whether the subject matter of a claim is supported by the disclosure of an application as filed, taken with the knowledge of those skilled in the art. MPEP 7th ed., rev. 2 § 2163.01; *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1576 (Fed. Cir. 1985). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, “Written Description” Requirement, 66 FR 1099, 1105, Jan. 5, 2001 (citing *In re Wertheim*, 541 F.2d 257 (CCPA 1976)). Thus, the Patent Office has the burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976); MPEP §2163.04.

To satisfy the written description requirement, the specification must convey with reasonable clarity to one of skill in the art that the applicant was in possession of the invention at the time of filing the application. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). An applicant can demonstrate possession by describing sufficient relevant identifying characteristics. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, “Written Description” Requirement at 1101, 1104, 1105; *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Such characteristics include “i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, “Written Description” Requirement at 1106. In addition, possession can be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, “Written Description” Requirement at 1101, 1104, 1105-06; *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1565 (Fed. Cir. 1991); *Autogiro Co. of America v. United States*, 384 F.2d 391, 398 (Ct. Cl. 1967); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Thus, “[a]n applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.” Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, , first

paragraph, "Written Description" Requirement at 1104 (quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d at 1572 (Fed. Cir. 1997)).

That which is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement at 1106 (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). Furthermore, the written description requirement does *not* require an actual reduction to practice. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement at 1101, 1105 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1576 (Fed. Cir. 1985); *Pfaff v. Wells Electronics, Inc.*, 525 US 55, 66 (1998)). Accordingly, an applicant need not show that the invention will work for its intended purpose to satisfy the written description requirement.

Contrary to the Examiner's position, the specification thoroughly describes the claimed method of the invention. The specification teaches a process for directly producing desacetylcephalosporin C using a host cell containing recombinant nucleic acid having a sequence coding for all or part of cephalosporin esterase from *Rhodospiridium*. A representative (and preferred) source of the esterase nucleic acid is *Rhodospiridium toruloides* ATCC 10657 which is publicly available. See, for instance, page 3, line 29 to page 4, line 3 of the specification. However, naturally occurring allelic variants of the esterase may be present in *Rhodospiridium* and these variants are within the scope of the claimed invention. See, for instance, page 4, line 20-25, of the specification, describing the existence of allelic variants. Methods of obtaining recombinant nucleic acid molecules are well-known in the art. For instance, genomic or cDNA libraries can be screened to identify sequences coding for all or part of the cephalosporin esterase. See, for instance, page 5, line 3 to page 6, line 23, of the specification, describing methods for obtaining nucleic acid sequences that encode the esterase. Various mutants of the nucleic acid sequence encoding the esterase are also within the scope of the invention. These mutations may be degenerate or non-degenerate. Such modifications can be prepared by intentionally mutating the cephalosporin DNA sequence so as to cause a substitution, insertion, inversion, or addition of one or more amino acids in the encoded esterase polypeptide using techniques that are well-known in the art. See, for instance, page 6, line 24 to page 7, line 16; and page 13, line 9 to page 14, line 19, of the specification. Moreover, due to the degenerate nature of the genetic code which results from there being more than one codon for

most of the amino acid residues, other nucleic acid sequences which encode the same amino acid sequence may be used for producing the esterase. See, for instance, page 13, line 9 to page 14, line 19, of the specification.

The specification also provides methods for ascertaining the physicochemical characteristics of esterases such as specific activity, substrate preferences, temperature and pH effects, and modulator effects. See, for instance, page 19 to page 24 of the specification. The specification further provides details regarding cloning of an esterase gene from *Rhodospiridium*, preparation of genomic libraries, clone selection, cDNA cloning, nucleotide sequence determination. See, for instance, Example 3 on pages 24-27. In addition, the specification provides details regarding vector construction (Example 4), transformation procedures (Example 5), and desacetylcephalosporin C culture procedure and expression detection (Example 6). Thus, one of skill in the art would readily be able to determine which *Rhodospiridium* cephalosporin esterases are capable of satisfying the conditions of the claims based on the teachings of the specification.

For all of the reasons discussed above, the specification fully describes the subject matter of the claims in such a way as to convey that the inventor had possession of the invention when the application was filed. Accordingly, the rejection of claims 1, 3-6, and 8-10 on the basis of the written description requirement of 35 U.S.C. § 112, first paragraph, must be withdrawn. Moreover, the Applicants respectfully submit that the 35 U.S.C. § 112, first paragraph, rejection cannot be applied against new claims 14-16 for at least the same reasons discussed above.

#### **IV. Rejection under 35 U.S.C. § 112, first paragraph (Enablement)**

Claims 1, 3-6 and 8-10 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The basis for the rejection can be found on pages 3 and 4 of the office action. Specifically, the Examiner alleged that while the specification is enabling for *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodospiridium* cephalosporin C esterase of SEQ ID NO:2, including nucleic acids of SEQ ID NOs:1 and 3, no enablement for a method of use with a strain of *Acremonium chrysogenum* transformed with nucleic acid encoding a *Rhodospiridium* cephalosporin C esterase having unknown homology for SEQ ID NOs:1 or 3. Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 112, all that is required is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. The Federal

Circuit has established that the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed Cir. 1988); *US v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The law clearly states that “a considerable amount of experimentation is permissible, if it is merely routine.” *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed Cir. 1985); MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int’l Trade Comm’n 1983). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The specification teaches a process for directly producing desacetylcephalosporin C using a host cell containing recombinant nucleic acid having a sequence coding for all or part of cephalosporin esterase from *Rhodospiridium*. A representative (and preferred) source of the esterase nucleic acid is *Rhodospiridium toruloides* ATCC 10657 which is publicly available. See, for instance, page 3, line 29 to page 4, line 3. However, naturally occurring allelic variants of the esterase may be present in *Rhodospiridium* and these variants are within the scope of the claimed invention. See, for instance, page 4, line 20-25, of the specification, describing the existence of allelic variants. Methods of obtaining recombinant nucleic acid molecules are well-known in the art. For instance, genomic or cDNA libraries can be screened to identify sequences coding for all or part of the cephalosporin esterase. See, for instance, page 5, line 3 to page 6, line 23, of the specification, describing methods for obtaining nucleic acid sequences that encode the esterase. Various mutants of the nucleic acid sequence encoding the esterase are also within the scope of the invention. These mutations may be degenerate or non-degenerate. Such modifications can be prepared by intentionally mutating the cephalosporin DNA sequence so as to cause a substitution, insertion, inversion, or addition of one or more amino acids in the encoded esterase polypeptide using techniques that are well-known in the art. See, for instance, page 6, line 24 to page 7, line 16; and page 13, line 9 to page 14, line 19, of the specification. Moreover, due to the degenerate nature of the genetic code which results from there being more than one codon for most of the amino acid residues, other nucleic acid sequences which encode

the same amino acid sequence may be used for producing the esterase. See, for instance, page 13, line 9 to page 14, line 19.

The specification also provides methods for ascertaining the physicochemical characteristics of esterases such as specific activity, substrate preferences, temperature and pH effects, and modulator effects. See, for instance, page 19 to page 24 of the specification. The specification further provides details regarding cloning of an esterase gene from *Rhodospiridium*, preparation of genomic libraries, clone selection, cDNA cloning, nucleotide sequence determination. See, for instance, Example 3 on pages 24-27. In addition, the specification provides details regarding vector construction (Example 4), transformation procedures (Example 5), and desacetylcephalosporin C culture procedure and expression detection (Example 6). Thus, one of skill in the art would readily be able to determine which *Rhodospiridium* cephalosporin esterases are capable of satisfying the conditions of the claims based on the teachings of the specification.

The Examiner alleges that trial and error experimentation would be necessary to practice the invention. However, Applicants point out that a considerable amount of experimentation is permissible, if it is merely routine. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed Cir. 1985); MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Using the methods known in the art described above and those described in the instant application, a skilled artisan could easily identify and screen a variety of nucleic acid sequences encoding *Rhodospiridium* cephalosporin esterase as a matter of routine experimentation.

For all of the reasons discussed above, the specification teaches one skilled in the art how to make and use the claimed invention. Applicants teach the method of making desacetylcephalosporin C using cells having nucleic acids that encode cephalosporin C biosyntheses enzymes and recombinant nucleic acids encoding *Rhodospiridium* cephalosporin esterase. Further, the specification provides an example using a *Rhodospiridium* available from ATCC to show that direct production of desacetylcephalosporin C from an engineered *Acremonium* is possible. Therefore, the specification teaches one of skill in the art how to use the engineered *Acremonium chrysogenum* without undue experimentation. Accordingly,

Applicants submit that new claims 14-16 cannot be rejected on the basis of the enablement requirement of 35 U.S.C. § 112, first paragraph.

**V. Rejection under 35 U.S.C. § 102(b) based on Politino**

Claims 1-13 were rejected under 35 U.S.C. § 102(b) as being anticipated by Politino et al (WO 98/12345)(“Politino A”). Specifically, the Examiner alleged that Politino A teaches (1) DNA encoding cephalosporin C esterase from *Rhodospiridium toruloides* that is 100% identical to SEQ ID NOs:1 or 3 of the application; (2) a method of producing cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed with DNA encoding cephalosporin esterase from *Rhodospiridium toruloides*; (3) cells are cultured under conditions of 22°C to about 29°C and PH of about 5.5 to about 7.5; (4) *Cephalosporin acremonium* (*Acremonium chrysogenum*) produces cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosyntheses; (5) when cephalosporin C esterase from *Rhodospiridium toruloides* is added, desacetylcephalosporin C is produced (Example 2); (6) Cephalosporin C is completely hydrolyzed by esterase with 30 minutes at 30°C, pH 6.5 with no side products; (7) that conditions of 30°C that is about 29°C and pH 6.5 is in the range of about 5.5 to about 7.5. Politino A is also alleged to teach chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC. On this basis, the Examiner alleged that the presently claimed invention is anticipated. The Applicants respectfully traverse this rejection.

As a general rule, for prior art to anticipate under § 102, every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumitomo Electric*, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Applicants respectfully submit that Politino A cannot be applied to support an anticipation rejection of the claims under 35 U.S.C. § 102 (b).

Contrary to the Examiner’s position, Politino A does not teach any cell-based method for producing desacetylcephalosporin C. Furthermore, Politino A does not teach any cell-based method that employs using cells having nucleic acids that encode cephalosporin C biosyntheses enzymes and recombinant nucleic acids encoding *Rhodospiridium* cephalosporin esterase as presently claimed.

First, the Examiner alleged that Politino A disclosed DNA encoding cephalosporin C esterase from *Rhodospiridium toruloides* that is 100% identical to SEQ ID NOs:1 or 3 of the application. Assuming arguendo that the Examiner's assertion is true, a disclosure of DNA having 100% identity to SEQ ID NOs:1 or 3 is not a disclosure of the Applicants' claimed cell-based method for directly producing desacetylcephalosporin C.

Second, the Examiner also alleged that Politino A disclosed a method of producing cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed with DNA encoding cephalosporin esterase from *Rhodospiridium toruloides*, citing to page 9 and claims 26-28. However, contrary to the Examiner's assertion, Politino A's claims 26-28 are directed to a "method for producing a polypeptide having cephalosporin esterase activity," not to a cell-based method for directly producing desacetylcephalosporin C as presently claimed. Moreover, page 9 of Politino A described host cells that express a polypeptide having cephalosporin esterase activity for the purpose of producing large amounts of the desired polypeptide. See also Politino A's abstract. Thus, Politino A is completely silent with respect to any method for directly producing desacetylcephalosporin C as presently claimed.

Third, the Examiner alleged that cells are cultured under conditions of 22°C to about 29°C and pH of about 5.5 to about 7.5. The Examiner, however, has failed to provide the location in Politino A to support the assertion. Moreover, in reviewing the entire disclosure of Politino A, the Applicants cannot find any disclosure of any cell culturing conditions. Thus, contrary to the Examiner's position, Politino A does not teach the temperature and pH ranges as recited in the present claims.

Fourth, the Examiner further alleged that *Cephalosporin acremonium* (*Acremonium chrysogenum*) produces cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosyntheses. However, Politino A does not discuss any functional properties of *Cephalosporin acremonium*, instead focusing on *Rhodospiridium toruloides* as the source of cephalosporin C esterase activity. See col. 1 under "Background of the invention" and Example 1 in Politino A. Thus, Politino A cannot be applied as a 102(b) reference to support the Examiner's assertion. However, assuming arguendo that the Examiner's assertion is true, a disclosure of DNA having 100% identity to SEQ ID NOs:1 or 3 is not a disclosure of the Applicants' claimed cell-based method.

Fifth, the Examiner also alleged that when cephalosporin C esterase from *Rhodospiridium toruloides* is added, desacetylcephalosporin C is produced (Example 2). In

reviewing Example 2 of Politino A's, the Applicants note that the entire example is directed to characterization of the cephalosporin esterase enzyme itself. In section 2.1, Politino A described a buffered reaction mixture containing a potassium salt of cephalosporin C. The cephalosporin esterase enzyme is added to the reaction mixture to initiate the enzyme reaction. Thereafter, the reaction is quenched and the reaction products are isolated and characterized. In section 2.2, Politino A ran additional reaction mixtures but used different ester substrates to evaluate a substrate profile for the cephalosporin esterase. Politino A ran additional reaction mixtures to determine the effect of temperature (section 2.3), pH (section 2.4) and modulators (section 2.5). In sections 2.6 and 2.7, Politino A determined the isoelectric point and molecular weight, respectively, of the cephalosporin esterase enzyme. In section 2.8, Politino A treated the cephalosporin esterase enzyme with endoglycosidase to determine carbohydrate content. Finally, Politino A determined the N-terminal amino acid sequence of cephalosporin esterase by automated Edman degradation. Nowhere in Example 2 does Politino A teach or suggest the presently claimed cell-based method involving direct production of desacetylcephalosporin C. Moreover, even if desacetylcephalosporin C is produced in the presence of cephalosporin C esterase as the Examiner would have it, such disclosure is not a disclosure of the presently claimed cell-based method for direct production of desacetylcephalosporin C.

In addition, the Examiner alleged that cephalosporin C is completely hydrolyzed by esterase with 30 minutes at 30°C, pH 6.5 with no side products. Although the Examiner failed to provide the location in Politino A of this assertion, the Applicants believe that the Examiner is relying on Example 2 (section 2.1) for the enzymatic assay conditions for measuring the specific activity of the free enzyme in the presence of added potassium salt of cephalosporin C, not cell culturing conditions. Accordingly, mere disclosure of that cephalosporin C does not form side products under free enzyme-based conditions is not a disclosure of a cell-based method of directly producing desacetylcephalosporin C as presently claimed. Indeed, Smith (U.S. Patent no. 4,533,632 cited by the Examiner elsewhere in the Office action) notes that under cell-based fermentation conditions, cephalosporin C undergoes degradation. See, for instance, Smith at col. 1, lines 42-55.

Next, the Examiner alleged that that conditions of 30°C is about 29°C and pH 6.5 is in the range of about 5.5 to about 7.5. Again, it appears that the Examiner is relying on Example 2 (section 2.1) for the enzymatic assay conditions for measuring the specific activity of the free enzyme in the presence of added potassium salt of cephalosporin, not cell culturing conditions.

Accordingly, a disclosure of an enzyme-based assay conditions for complete hydrolysis of cephalosporin C in an enzymatic assay solution is not a disclosure of a cell-based method of directly producing desacetylcephalosporin C as presently claimed.

Finally, the Examiner alleged that Politino A teaches chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC. The applicants again believe that the Examiner is relying on Example 2 (section 2.1) which describes an enzyme-based reaction for measuring enzyme specific activity, not a cell-based method for directly producing desacetylcephalosporin C as presently claimed. Reaction products were isolated from a free enzyme assay mixture, not fermentation broth. In reviewing Example 2, Politino A does not teach the aforementioned assertion. Moreover, assuming arguendo that what the Examiner assertion is true, a disclosure of chemical breakdown of cephalosporin in the recited ranges in an enzymatic assay solution is not a disclosure of a cell-based method of directly producing desacetylcephalosporin C as presently claimed.

In view the above discussion, the Applicants submit that withdrawal of the § 102(b) rejection against claims 1,3-6, and 9-11 based on Politino A is in order and is respectfully requested. Politino A is directed to enzyme-based methods and methods for producing enzyme, not a cell-based method for direct production of desacetylcephalosporin C as presently claimed, and therefore cannot support a rejection under § 102(b). The Applicants also submit that Politino A cannot be applied to support a § 102(b) rejection of new claims 14-16 for at least the same reasons discussed above.

#### **VI. Rejection under 35 U.S.C. § 102(e) based on Politino**

Claims 1, 3-6 and 9-11 were rejected under 35 U.S.C. § 102(e) as being anticipated by Politino et al (U.S. Patent no. 5,869,309)(“Politino B”). Specifically, the Examiner alleged that Politino A teaches (1) DNA encoding cephalosporin C esterase from *Rhodospiridium toruloides* that is 100% identical to SEQ ID NOs:1 or 3 of the application; (2) a method of producing cephalosporin C esterase by culturing cells of *Cephalosporin acremonium* transformed with DNA encoding cephalosporin esterase from *Rhodospiridium toruloides*; (3) cells are cultured under conditions of 22°C to about 29°C and PH of about 5.5 to about 7.5; (4) *Cephalosporin acremonium* (*Acremonium chrysogenum*) produces cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosyntheses; (5) when cephalosporin C esterase from

*Rhodospiridium toruloides* is added, desacetylcephalosporin C is produced (Example 2); (6) Cephalosporin C is completely hydrolyzed by esterase with 30 minutes at 30°C, pH 6.5 with no side products; (7) that conditions of 30°C that is about 29°C and pH 6.5 is in the range of about 5.5 to about 7.5. Politino A is also alleged to teach chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% as required by claims 1 and 3-6 because no side products were observed by HPLC. On this basis, the Examiner alleged that the presently claimed invention is anticipated. The Applicants respectfully traverse this rejection.

The Applicants note that the Examiner's basis for the § 102(e) rejection is identical to the §102(b) rejection discussed above. The Applicants further note that the specifications of Politino A and B are essentially the same. Accordingly, the Applicants incorporate the discussion regarding the § 102(b) rejection herein and submit that the § 102(e) rejection of claims 1, 3-6, and 9-11 based on Politino B is improper and should be withdrawn. The Applicants also submit that Politino B cannot be applied to support a § 102(e) rejection of new claims 14-16 for at least the same reasons discussed above.

#### **VII. Rejection under 25 U.S.C. § 103(a) based on Politino A or B in view of Smith**

Claim 8 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Politino A or B in view of Smith (U.S. Patent No. 4,533,632). The Examiner alleged that Smith teaches a process for preparing desacetylcephalosporin C by fermenting *Acremonium chrysogenum* in the presence of esterase from *Rhodospiridium toruloides* and that the fermentation process is carried out at 15 to 45°C and pH 4-9. The Examiner asserts it would have been obvious to employ *Acremonium chrysogenum* transformed with DNA encoding *Rhodospiridium toruloides* esterase based on Politino A or B teachings in a method for increase and standardizing production of esterase in Smith's method. The Applicants respectfully traverse this rejection.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5

U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Contrary to the Examiner's position, the Applicants respectfully submit that neither Politino A or B and Smith, alone or in combination, teach or suggest what the Applicants have done.

The present invention relates to a process for the direct production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodospiridium* cephalosporin esterase under conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. The use of the recombinant *Acremonium chrysogenum* fungal organism results in direct production of desacetylcephalosporin C from cephalosporin C and further without substantial loss of cephalosporin C due to non-enzymatic breakdown which normally results from fermentation broth.

Contrary to the Examiner's position, Politano A or B are directed to isolated cephalosporin esterase, nucleic acids encoding the esterase from *Rhodospiridium* including expression vectors, host cells transformed with the expression vectors, and methods for producing cephalosporin esterase. See Politino A and B abstracts. Example 1 of Politino A and B describes culturing *Rhodospiridium toruloides* (section 1.1) and extracting cephalosporin esterase from *Rhodospiridium toruloides* (section 1.2). Example 2 (discussed above in section V) relates cell-free enzyme-based reaction solutions for measuring specific activity, substrate profiles, temperature/thermal stability/pH/modulator effects, determination of isoelectric point/molecular weight/carbohydrate content/N-terminal amino acid sequence of the cephalosporin esterase. Example 3 describes preparation of chromosomal DNA of *Rhodospiridium toruloides* (section 3.0), genomic DNA library construction (section 3.1), clone selection (section 3.2), cDNA cloning (section 3.3) and nucleotide sequencing (section 3.4). As shown in these examples, Politino A and B are directed to isolated esterase-based methods and to methods for producing enzyme. Thus, both Politino A and B are concerned with the problem of producing pure isolated cephalosporin esterase and provided a solution to this problem. Indeed, both Politino A and B are completely silent with respect to any method for direct production of

desacetylcephalosporin C as presently claimed. Smith does not remedy Politino A and B's teachings.

Smith describes a method of fermenting cephalosporin C-producing microorganisms, e.g., *Acremonium chrysogenum*, in the presence of added acetylcetase enzyme so that cephalosporin C formed is converted into desacetylcephalosporin C. See abstract. The acetylcetase, as a separate bioreagent, is added at some point during the fermentation process. See Smith at col. 2, lines 14-28; col. 3, lines 56-68. While Smith does describe conducting fermentation at 15-45°C and pH 4.9, such disclosure relates to a method involving addition of esterase enzyme into a fermentation broth containing a cephalosporin C-producing microorganism and is not a disclosure of a method for directly producing desacetylcephalosporin C from a *Acremonium chrysogenum* strain having nucleic acid encoding cephalosporin C biosynthesis enzymes and a recombinant nucleic acid encoding *Rhodospiridium* cephalosporin esterase. Thus, Smith alone or in combination with Politino A or B is not prior art under 35 U.S.C §103(a) against the claims. Withdrawal of the §103(a) rejection is in order and is respectfully requested. The Applicants further submit that the § 103(a) rejection based on Politano A or B in view of Smith cannot be applied to reject new claims 14-16.

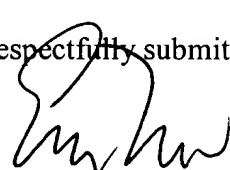
### VIII. Conclusion

In view of the above remarks and amendments, the Applicants respectfully submit that the application is considered to be in good and proper form for allowance and requests that the Examiner pass this application to issue. If the Examiner believes that a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Dated: Sept. 30, 2005

McDonnell Boehnen  
Hulbert & Berghoff LLP  
300 South Wacker Drive  
Chicago, IL 60606  
Telephone: 312-913-0001  
Facsimile: 312-913-0002

Respectfully submitted,

  
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Emily Mao  
Reg. No. 35,285